## AMENDMENTS TO THE SPECIFICATION

Please add the following text to page 1 after the title "PHARMACEUTICAL COMPOSITIONS WITH SYNCHRONIZED SOLUBILIZER RELEASE" and before the paragraph entitled "1. Technical Field:"

**Priority Data**

"This application is a continuation in part of U.S. Patent App. No. 10/428,341 filed on May 1, 2003, now issued as U.S. Patent No. 6,923,988, which is a continuation of U.S. Patent App. No. 09/800,593 filed on March 6, 2001, now issued as U.S. Patent No. 6,569,463, which is a division of U.S. Patent App. No. 09/447,690, now issued as U.S. Patent No. 6,248,363."

Please amend the third paragraph beginning on page 8 of the specification to read as follows:

Examples of drugs which may benefit from synchronized release of drug and solubilizer include, without limitation, acebutolol, alfaxalone, amlodipine, amiodarone, amprenavir, anastrazole, atenolol, atovaquone, atorvastatin, avasimibe, azathioprine, beclomethasone, betaxolol, bicalutamide, bisoprolol, bosentan, bucindolol, budesonide, buproprion, carvedilol, candesartan, carbamezepine, carbadopa, celecoxib, cetirizine, chenodeoxycholic acid, ciclesonide, cilostazol, cipofloxacin, citalopram, clobetasol, clopidogrel, dehydroepiandrosterone, dehydroepiandrosterone sulfate, delaviridine, desogestrel, dihydroergotamine, dianabol, dilevalol, dipyridamole, docetaxel, donezepil, desloratadine, dutasteride, efivarenz, enlopitant, entacapone, eplerenone, eprosartan, ergotamine, esmolol, etoprolol, etoricoxib, everolimus, ~~fenofibate~~ fenofibrate, fexofenadine, fluphenazine, frovatriptan, granisetron, hydrocodone, isradipine, itasetron, labetalol, lamotrigine, lansoprazole, lercanidipine, letrozole, levadopa, levofloxacin, loratadine, lovastatin, mefloquin, metaxolone,

metolazone, mifepristone, mirtazapine, modafinil, morphine, mometasone, nadalol, nefazodone, nevibulol, nifedipine, nefinavir, nimodipine, nisoldipine, norethindrone, norethindrone acetate, nortestosterone, olanzapine, ondasetron, oxacarbezine, oxaprozin, oxprenolol, paroxetine, pergolide, phenazopyridine, pioglitazone, pimecrolimus, pitavastatin, pregnanediol, pregnanolone, pregnenolone, allopregnanolone, epiallopregnanolone, progesterone, propafenone, propanolol, ramipril, ranolazine, risperidone, ritanovir, rivastigmine, rofeconxib, ropinorole, rosiglitazone, rosuvastatin, salmeterol, saquinavir, sertraline, sildenafil, sotalol, simvastatin, sparfloxacin, spironolactone, stavudine, sumatriptan, tadalafil, tegaserod, tamsulosin, terbinafine, testosterone and testosterone esters, methyltestosterone, thalidoamide, tiagabine, tibolone, tizanidine, tolcapone, topiramate, trandolapril, tramadol, valdecoxib, vardenafil, valsartan, valrubicin, ursodeoxycholic acid, voriconazole, zafirlukast, zalepelon, zileuton, ziprasidone, and zolpidem. Some preferred drugs are cilostazol, carvedilol, zafirlukast, amiodarone, fenofibrate, dronederone, risperdone, ziprasidone, simivastatin, pioglitazone or atorvastin.

Please amend the first paragraph beginning on page 10 of the specification to read as follows:

Due to pH dependent solubility characteristics orally administered carvedilol pharmaceutical compositions may provide significant carvedilol solubility and release in the stomach due to the low pH, thus leading to elevated or rapidly increasing plasma concentrations and hypotensive side-effects. As the formulation moves through gastrointestinal tract and the pH rises, carvedilol solubility and release becomes negligible. As a result, ~~caravedilol~~ carvedilol is required to be administered with food to delay initial release in the stomach and to reduce the potential for hypotensive adverse effects. These characteristics make carvedilol particularly well-suited for formulation in synchronized solubilizer release compositions.

Please amend the fourth paragraph beginning on page 11 of the specification to read as follows:

Preferred fatty acids and alcohols are the $C_6$-$C_{22}$ fatty acids and alcohols, such as stearyl alcohol, capric acid, caprylic acid, lauric acid, myristic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachnidoic acid, behenic acid, and their corresponding pharmaceutically acceptable salts. Preferred fatty acid and fatty alcohol derivatives include sodium dioctyl sulfosuccinate, sodium lauryl sulfate, amide esters (e.g., lauric acid diethanolamide, sodium lauryl sarcosinate, lauroyl carnitine, palmitoyl carnitine and myristoyl carnitine), esters with hydroxy-acids (e.g., sodium stearoyl lactylate); sugar esters [e.g., lauryl lactate, glucose monocaprylate, diglucose monocaprylate, sucrose laurate, sorbitan monolaurate (~~Arlacel®~~ARLACEL® 20), sorbitan monopalmitate (Span-40), sorbitan monooleate (Span-80), sorbitan monostearate and sorbitan tristearate], lower alcohol fatty acid esters [e.g., ethyl oleate (Crodamol EO), isopropyl myristate (Crodamol IPM) and isopropyl palmitate (Crodamol IPP)], esters with propylene glycol [e.g., propylene glycol monolaurate (Lauroglycol FCC), propylene glycol ricinoleate (Propymuls), propylene glycol monooleate (~~Myverol~~MYVEROL® P-O6), propylene glycol monocaprylate (~~Capryol~~CAPRYOL® 90), propylene glycol dicaprylate/dicaprate (~~Captex~~CAPTEX® 200) and propylene glycol dioctanoate (~~Captex~~ CAPTEX® 800)], esters with glycerol [e.g., glyceryl monooleate (Peceol), glyceryl ricinoleate, glyceryl laurate, glyceryl dilaurate (~~Capmul~~CAPMUL® GDL), glyceryl dioleate (~~Capmul~~ CAPMUL® GDO), glycerol monolinoleate (~~Maisine~~MAISINE®), glyceryl mono/dioleate (~~Capmul~~ CAPMUL® GMO-K), glyceryl caprylate/caprate (~~Capmul~~ CAPMUL® MCM), caprylic acid mono/diglycerides (~~Imwitor~~IMWITOR® 988), mono- and diacetylated monoglycerides (~~Myvacet~~MYVACET® 9-45)], triglycerides [e.g., corn oil, almond oil, soybean

oil, coconut oil, castor oil, hydrogenated castor oil, hydrogenated coconut oil, Pureco 100, Hydrokote AP5, ~~Captex~~ CAPTEX® 300, 350, Miglyol 812, Miglyol 818 and ~~Gelucire~~GELUCIRE® 33/01)], mixtures of propylene glycol esters and glycerol esters [e.g., mixture of oleic acid esters of propylene glycol and glycerol (~~Arlacel~~ARLACEL® 186)], and polyglycerized fatty acids such as polyglyceryl oleate (~~Plurol~~PLUROL® Oleique), polyglyceryl-2 dioleate (Nikkol DGDO), polyglyceryl-10 trioleate, polyglyceryl-10 laurate (Nikkol Decaglyn 1-L), polyglyceryl-10 oleate (Nikkol Decaglyn 1-O), and polyglyceryl-10 mono, dioleate (~~Caprol~~CAPROL® PEG 860).

Please amend the first paragraph beginning on page 12 of the specification to read as follows:

Other useful fatty acid derivatives include polyethoxylated fatty acids, (e.g., PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate and PEG-20 oleate), PEG-fatty acid diesters (e.g., PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate and PEG-32 dioleate), PEG-fatty acid mono- and di-ester mixtures, polyethylene glycol glycerol fatty acid esters (e.g., PEG'ylated glycerol 12-acyloxy-stearate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate and PEG-30 glyceryl oleate) and alcohol-oil transesterification products [e.g., polyoxyl 40 castor oil (~~Cremophor~~®CREMOPHOR® RH40), polyoxyl 35 castor oil (~~Cremophor~~ CREMOPHOR® EL or ~~Incrocas~~ INCROCAS® 35), PEG-25 trioleate (TAGAT® TO), PEG-60 corn glycerides (Crovol M70), PEG-60 almond oil (Crovol A70), PEG-40 palm kernel oil (Crovol PK70), PEG-50 castor oil (Emalex C-50), PEG-50 hydrogenated castor oil (Emalex HC-50), PEG-60 hydrogenated castor oil (~~Cremophor~~CREMOPHOR® RH60), PEG-8 caprylic/capric glycerides

(~~Labrasol~~®LABRASOL®), lauroyl macrogol-32 glycerides (~~Gelucire~~GELUCIRE® 44/14), linoleoyl ~~macrogoglycerides~~ macrogolglycerides (~~Labrafil~~®LABRAFIL®), stearoyl macrogol-32 glycerides (~~Gelucire~~GELUCIRE® 50/13), and PEG-6 caprylic/capric glycerides (~~Softigen~~®SOFTIGEN® 767)].

Please amend the second paragraph beginning on page 13 of the specification to read as follows:

Bile acid and sterol derivatives include, but are not limited to, cholate, ursodeoxycholate, chenodeoxycholate, taurochenodeoxycholate, tauroursodeoxycholate, glycochenodeoxycholate, glycoursodeoxycholate, sterols and sterol esters or ethers such as PEG-24 cholesterol ether (~~Solulan~~SOLULAN® C-24).

Please amend the fourth paragraph beginning on page 13 of the specification to read as follows:

Preferred solubilizers include polyoxyl 40 castor oil, polyoxyl 35 castor oil, PEG-8 caprylic/capric glycerides (~~Labrasol~~®LABRASOL®), sorbitan monooleate (Span-80), sorbitan monolaurate (Span 20), PEG-20 sorbitan monopalmitate (Tween 40), PEG-20 sorbitan monostearate (Tween 60), PEG-20 sorbitan monooleate (polysorbate 80 or Tween 80), glyceryl mono/dioleate (~~Capmul~~CAPMUL® GMO-K), glyceryl caprylate/caprate (~~Capmul~~CAPMUL® MCM), caprylic acid mono/diglycerides (~~Imwitor~~IMWITOR® 988), and mono- and diacetylated monoglycerides (~~Myvacet~~MYVACET® 9-45), linoleoyl monoglycerides (~~Labrafil~~LABRAFIL® 2125CS), lauroyl macrogol-32 glycerides (~~Gelucire~~GELUCIRE® 44/14), α-tocopherol, α-tocopherol acetate, α-tocopherol succinate, α-tocopherol polyethyleneglycol (200-8000 MW) succinate, α-tocopherol polyethylene glycol 400 succinate, d1-α-tocopherol polyethyleneglycol 1000 succinate, and d-α-tocopherol polyethyleneglycol 1000 succinate.

Please amend the first paragraph beginning on page 14 of the specification to read as follows:

Particularly preferred solubilizers include polyoxyl 40 castor oil, polyoxyl 35 castor oil, sorbitan monooleate, PEG-20 sorbitan monooleate (polysorbate 80 or Tween 80), linoleoyl mononglycerides (~~Labrafil~~LABRAFIL® 2125CS), lauroyl macrogol-32 glycerides (~~Gelucire~~GELUCIRE® 44/14) and d-α-tocopherol polyethyleneglycol 1000 succinate.

Please amend the second paragraph beginning on page 15 of the specification to read as follows:

Specific examples of fatty acids or fatty alcohols and derivatives useful as release modulators include, but are not limited to, stearyl alcohol, stearic acid, hydrogenated vegetable oil, glycerol dibehenate (~~Compritol®~~COMPRITOL® 888), glycerol distearate (~~Precirol~~PRECIROL®), lauroyl macrogol-32 glycerides (~~Gelucire~~GELUCIRE® 44/14), and stearoyl macrogol-32 glycerides (~~Gelucire~~GELUCIRE® 50/13), sodium steroyl lactylate, calcium steroyl lactylate, stearic acid, sucrose distearate, sucrose palmitate, sucrose dipalmitate and waxes (e.g., the mixed fatty alcohol and fatty acid derivative waxes like cetyl esters wax, nonionic emulsifying wax, yellow wax, white wax, and carnauba wax). Preferred fatty acids, fatty alcohols, or derivatives include hydrogenated vegetable oil, glycerol dibehenate, glycerol distearate, glycerol dipalmitate, glycerol ~~palmitosearate~~ palmitostearate, lauroyl macrogol-32 glyceride, stearoyl macrogol-32 glyceride, calcium steroyl lactylate, stearic acid, stearoyl alcohol, sucrose distearate, sucrose palmitate, sucrose dipalmitate, carnauba wax, yellow wax, white wax, or cetyl ester wax.

Please amend the third paragraph beginning on page 15 of the specification to read as follows:

Specific examples of tocol derivatives useful as release modulators include, but are not limited to, the mono-, di-, trimethyl-tocols, commonly known as tocopherols, and the organic acid esters thereof (e.g., acetate, nicitanoate, succinate, ~~polyethylnene~~ polyethylene glycol succinate esters, etc.). For example, α-tocopherol, α-tocopherol acetate, α-tocopherol nicotinate, α-tocopherol succinate, α-tocopherol polyethyleneglycol (200-8000 MW) succinate, α-tocopherol polyethylene glycol 400 succinate are specific compounds useful as release modulators. The mixed racemic forms (e.g. all racemic or dl-), and the pure enantiomers (e.g. d-, l- or RRR-) of tocol derivatives are all useful in practicing the current invention.

Please amend the first paragraph beginning on page 16 of the specification to read as follows:

Many release modulators can additionally serve as solubilizers for the drug either in the pharmaceutical composition or in aqueous dispersions (also act as a solubilizer, as defined in the previous section). Similarly, many solubilizers can additionally serve as release modulators for the drug either in the pharmaceutical composition or in aqueous dispersions (also act as a release modulator, as defined above).

Please amend the fourth paragraph beginning on page 16 of the specification to read as follows:

Suitable additives include those commonly utilized to facilitate processing steps such as agglomeration, air suspension chilling, air suspension drying, balling, coacervation, comminution, compression, pelletization, cryopelletization, extrusion, granulation, homogenization, inclusion complexation, lyophilization, nanoencapsulation[.], melting, mixing, molding, pan coating, solvent dehydration, sonication, spheronization, spray chilling, spray

congealing, spray drying, or other processes known in the art. The additive can also be pre-coated or encapsulated. Appropriate coatings are well known in the art.

Please amend the fifth paragraph beginning on page 16 of the specification to read as follows:

The pharmaceutical compositions of the present invention can optionally include one or more solvents, i.e., additives, to increase the solubility of the active ingredient or other composition components in the carrier, as distinct from solubilizers that increase aqueous solubility of the drug. Suitable solvents for use in the compositions of the present invention include without limitation, acids (e.g., acetic acid, propionic acid, butyric acid, lactic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, etc.), alcohols and polyols, (e.g., ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, cellulose derivatives, etc.), ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000 (e.g., tetrahydrofurfuryl alcohol PEG ether (glycofurol, available commercially from BASF under the trade name ~~Tetraglycol~~TETRAGLYCOL®) or methoxy PEG (Union Carbide)) amides, (e.g., 2-pyrrolidone, 2-piperidone, caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethyl acetamide, polyvinylpyrrolidone etc.), esters (e.g., ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, caprolactone and isomers thereof, valerolactone and isomers thereof, butyrolactone and isomers thereof, etc.) and other solvents

known in the art, such as dimethyl acetamide, dimethyl isosorbide (Arlasolve DMI (ICI)), N-methylpyrrolidones (Pharmasolve (ISP)), monooctanoin and diethylene glycol monoethyl ether (available from Gattefosse under the trade name ~~Transcutol~~TRANSCUTOL®). Mixtures of solvents are also within the scope of the invention. These compounds are readily available from standard commercial sources or may be synthesized using procedures known to those of skill in the art.

Please amend the third paragraph beginning on page 17 of the specification to read as follows:

Other additives conventionally used in pharmaceutical compositions can be included, and these additives are well known in the art. Such additives include, but are not limited to, anti-adherents (anti-sticking agents, glidants, flow promoters, lubricants) (e.g., talc, magnesium stearate, fumed silica (Carbosil, Aerosil), micronized silica (Syloid No. FP 244, Grace U.S.A.), polyethylene glycols, surfactants, waxes, stearic acid, stearic acid salts, stearic acid derivatives, starch, hydrogenated vegetable oils, sodium benzoate, sodium acetate, leucine, PEG-4000 and magnesium lauryl sulfate) anticoagulants (e.g., acetylated monoglycerides), antifoaming agents (e.g., long-chain alcohols and silicone derivatives), antioxidants (e.g., BHT, BHA, gallic acid, propyl gallate, ascorbic acid, ascorbyl palmitate, 4-hydroxymethyl-2,6-di-tert-butyl phenol, tocopherol, etc.), binders (adhesives), i.e., agents that impart cohesive properties to powdered materials through particle-particle bonding, (e.g., matrix binders (dry starch, dry sugars), film binders (PVP, starch paste, celluloses, bentonite, sucrose)), chemical binders (e.g., polymeric cellulose derivatives, such as carboxy methyl cellulose, HPC, HPMC, etc., sugar syrups, corn syrup, water soluble polysaccharides (e.g., acacia, tragacanth, guar, alginates, etc.), gelatin, gelatin hydrolysate, agar, sucrose, dextrose, non-cellulosic binders (e.g., PVP, PEG, vinyl

pyrrolidone copolymers, pregelatinized starch, sorbitol, glucose, etc.), bufferants, where the acid is a pharmaceutically acceptable acid, (e.g., hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, etc.) and where the base is a pharmaceutically acceptable base, (e.g., an amino acid, an amino acid ester, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, or a pharmaceutically acceptable salt of acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, and uric acid, chelating agents (e.g., EDTA and EDTA salts), coagulants (e.g., alginates) colorants or opaquants, (e.g., titanium dioxide, food dyes, lakes, natural vegetable colorants, iron oxides, silicates, sulfates, magnesium hydroxide and aluminum hydroxide), coolants, (e.g. halogenated hydrocarbons (e.g., trichloroethane,

trichloroethylene, dichloromethane, fluorotrichloromethane), diethylether and liquid nitrogen) cryoprotectants (e.g., ~~trehelose~~ trehalose, phosphates, citric acid, tartaric acid, gelatin, dextran, mannitol, etc.), diluents or fillers, (e.g., lactose, mannitol, talc, magnesium stearate, sodium chloride, potassium chloride, citric acid, spray-dried lactose, hydrolyzed starches, directly compressible starch, microcrystalline cellulose, cellulosics, sorbitol, sucrose, sucrose-based materials, calcium sulfate, dibasic calcium phosphate and dextrose disintegrants or super disintegrants (e.g., croscarmellose sodium, starch, starch derivatives, clays, gums, cellulose, cellulose derivatives, alginates, crosslinked polyvinylpyrrolidone, sodium starch glycolate and microcrystalline cellulose), hydrogen bonding agents, (e.g., magnesium oxide), flavorants or desensitizers, (e.g., spray-dried flavors, essential oils and ethyl vanillin), ion-exchange resins (e.g., styrene/divinyl benzene copolymers, and quaternary ammonium compounds), plasticizers (e.g., polyethylene glycol, citrate esters (e.g., triethyl citrate, acetyl triethyl citrate, acetyltributyl citrate), acetylated monoglycerides, glycerin, triacetin, propylene glycol, phthalate esters (e.g., diethyl phthalate, dibutyl phthalate), castor oil, sorbitol and dibutyl seccate), preservatives (e.g., ascorbic acid, boric acid, sorbic acid, benzoic acid, and salts thereof, parabens, phenols, benzyl alcohol, and quaternary ammonium compounds), solvents (e.g., alcohols, ketones, esters, chlorinated hydrocarbons and water) sweeteners, including natural sweeteners (e.g., maltose, sucrose, glucose, sorbitol, glycerin and dextrins), and artificial sweeteners (e.g., aspartame, saccharine and saccharine salts) and thickeners (viscosity modifiers, thickening agents), (e.g., sugars, polyvinylpyrrolidone, cellulosics, polymers and alginates).

Please amend the third paragraph beginning on page 26 of the specification to read as follows:

Example 1 illustrates enhancement of the aqueous solubility of cilostazol with two representative solubilizers: a tocol derivative (Vitamin E Polyethylene Glycol Succinate, NF, or d-α-tocopherol polyethylene glycol 1000 succinate; ~~Vitamin~~ VITAMIN E TPGS®, Eastman Chemical Co.) [Example 1-1] and a polyethoxylated fatty acid derivative, (Polyoxyl 40 Hydrogenated Castor Oil, NF, ~~Cremophor~~CREMOPHOR® RH40; BASF) [Example 1-2]. Solutions of simulated intestinal fluid without enzyme (USP 26, pH 6.8) were prepared over a range of solubilizer concentrations. Excess cilostazol was added and equilibrated with gentle mixing at controlled temperature (37±0.5° C.). The aqueous solutions with excess drug were then filtered (0.2μ nominal pore size) and the clear filtrate was diluted and assayed by HPLC for cilostazol concentrations. Results are shown in FIG. 1.

Please amend the fourth paragraph beginning on page 26 of the specification to read as follows:

The intrinsic solubility of cilostazol under these conditions was 6.5 μg/ml, and solubility increased linearly with solubilizer concentration over the range tested. When d-α-tocopherol polyethylene glycol 1000 succinate was the solubilizer, the increase in solubility of cilostazol over its intrinsic aqueous solubility ranged from about a 60% increase at 0.05% w/v aqueous solubilizer concentration to about a 10-fold increase at 1% w/v aqueous solubilizer concentration. When ~~Cremophor~~CREMOPHOR® RH40, was the solubilizer, the solubility enhancement of cilostazol ranges from about a 30% increase at 0.05% w/v solubilizer concentration to about a 5-fold increase at 1% w/v aqueous solubilizer concentration.

Please amend the fourth paragraph beginning on page 30 of the specification to read as follows:

Example 5 illustrates synchronized solubilizer and cilostazol release from dosage forms prepared according to the current invention, using the solubilizers, d-alpha-tocopherol polyethylene glycol 1000 succinate and Linoleoyl Macrogolglycerides (~~Labrafil~~LABRAFIL® 2125CS). The release modulators were Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888 Ato, Gattefosse) and/or hydroxypropylmethylcellulose (Methocel K100M, Dow Chemical Company). The compositions of the prepared dosage forms are summarized below.

Please amend the first paragraph beginning on page 32 of the specification to read as follows:

Example 6 shows the performance of dosage forms prepared according to the current invention using Polyoxyl 40 Hydrogenated Castor Oil NF (~~Cremophor~~CREMOPHOR® RH40, BASF) as the solubilizer and hydroxypropyl methylcellulose (HPMC K4M,) as the release modulator. The compositions of the prepared dosage forms are summarized below.

Please amend the second paragraph beginning on page 32 of the specification to read as follows:

A binding solution of polyvinylpyrrolidone K90, ~~Cremophor~~CREMOPHOR® RH40, dehydrated alcohol USP, and deionized water was prepared and allowed to shake until all of the polyvinylpyrrolidone dissolved. Cilostazol was blended with talc, colloidal $SiO_2$ and the wetting agent, sodium dodecyl sulfate (Composition 3-2) and then passed through a 60 MESH screen. The microcrystalline cellulose and HPMC K4M were then added and blended in a polybag for ~20 minutes. The resulting powder was needed with the binder solution and the dough was extruded through the barrel of a 10 ml syringe. The extruded material was dried at 25°C/26-30% RH for about 20 hours. The dried extrusion was cut into pellets about 3-5 mm in length and filled into hard-gelatin capsules.

Please amend the fifth paragraph beginning on page 33 of the specification to read as follows:

Example 8 shows the enhancement of the solubility of the weakly basic antihypertensive, carvedilol, using various solubilizers in accordance with the present invention. The solubilizers were a polyethoxylated castor oil derivative (polyoxyl 35-castor oil, NF; ~~Cremophor~~®CREMOPHOR® EL, BASF), a tocol derivative (d-alpha tocopherol polyethylene glycol 1000 succinate, ~~Vitamin~~VITAMIN E TPGS®, Eastman Chemical Co.), a polyethoxylated fatty acid derivative (linoleyl macrogolglycerides, EP, ~~Labrafil~~LABRAFIL® 2125CS, Gattefosse). Composition 8-4 also includes a fatty acid derivative (Glycerol Dibehenate; ~~Compritol~~COMPRITOL® 888 Ato, Gattefosse). A control of carvedilol with no solubilizer was also prepared.

Please amend the first paragraph beginning on page 36 of the specification to read as follows:

A tablet dosage form according to the present invention was prepared containing carvedilol with d-alpha-tocopherol polyethylene glycol 1000 succinate as the solubilizer. Release modulators were a fatty acid derivative (Glycerol Dibehenate, ~~Compritol~~COMPRITOL® 888 Ato, Gattefosse), a cellulose derivative (HPMC K100LV and HPMC K4 MP, Dow Chemical Co.) and a polyacrylic (Carbopol 940, BF Goodrich) were used as the release modulators. The composition of the tablets is shown below.

Please amend the second paragraph beginning on page 36 of the specification to read as follows:

~~Compritol~~COMPRITOL® and ~~Vitamin~~VITAMIN E TPGS® were dry blended in an Osterizer blender, then the polymers and silica were added and blended in 4 stages. The resulting

mixture was sieved and the <60 MESH fraction collected. Carvedilol was added and the powder mixed for 8 hours on a wrist-action shaker with periodic mixing with a spatula (~1/hour).

Please amend the third paragraph beginning on page 36 of the specification to read as follows:

The final blend was compressed into tablets using a Carver press using IR pellet disks (12.5 mm diameter) at a force of 2,500 lb for 1-2 sec. The tablets were tested in a USP apparatus I at 100 rpm, 37.0±0.5°C. The dissolution medium was 1,000 ml simulated gastric fluid without enzyme (USP 26) for the first 2 hours, which was then replaced with 1,000 ml simulated intestinal fluid without enzyme for the remainder of the 24 hour experiment. Dissolution of carvedilol and the solubilizer ~~Vitamin~~VITAMIN E TPGS® were analyzed using an Agilent UV/Vis spectrophotometer with an on-line sample collection valve. Assay of carvedilol was based on absorbance at 360 nm and assay of ~~Vitamin~~VITAMIN E TPGS® was based on absorbance at 285 nm after subtraction of the carvedilol absorbance at this wavelength. Quantification was by linear regression of external standards of known carvedilol and ~~Vitamin~~VITAMIN E TPGS® concentration.

Please amend the second paragraph beginning on page 37 of the specification to read as follows:

A synchronized solubilizer release composition in accordance with the present invention was prepared using a tocol derivative as a solubilizer (~~Vitamin~~VITAMIN E-TPGS®, Eastman Chemical Company), a fatty acid derivative as a release modulator (~~Compritol~~COMPRITOL® 888 Ato, Gattefosse), and carvedilol in the proportions 75.2/18.8/6.0% w/w. ~~Vitamin~~VITAMIN E-TPGS® and ~~Compritol~~COMPRITOL® 888 were melted and blended together at 80°C., then carvedilol free base was dissolved in the mixture. The molten solution was filled into Size 3

hard-gelatin capsules at a fill weight of 0.21 mg/capsule (12.5 mg carvedilol/capsule) and allowed to solidify at ambient temperature (Example 10-1). Dissolution of carvedilol from these capsules was tested using 2 capsules each (25 mg carvedilol total) in a rotating bottle apparatus (Extended Release Tester; VanKel) at 10 rpm and 37±0.1°C. Dissolution media were 100 ml SGF without enzyme (pH 1.2, USP 26) or in 100 ml SIF without enzyme (pH 6.8, USP 26). A comparator formulation without synchronized solubilizer release was also tested under the same conditions (Comparator 10-1; ~~Coreg~~COREG® 25 mg carvedilol tablet; GlaxoSmithkline). Carvedilol release as a function of time was monitored as described in Example 8.

Please amend the first paragraph beginning on page 38 of the specification to read as follows:

The synchronized solubilizer release dosage form in Example 10 (Example 10-1) was dosed in a randomized, single-dose cross-over study in 7 healthy volunteers with a commercial immediate release tablet as a comparator (Comparator 11-1; ~~Coreg~~COREG® 12.5 mg carvedilol tablet; GlaxoSmithkline). Both treatments were administered immediately after breakfast. Blood samples of about 7 ml were collected in EDTA tubes, centrifuged, and the plasma assayed for carvedilol using a validated LC/MS/MS method. FIG. 7 shows the resulting plasma profiles and the table below shows the summary pharmacokinetic parameters calculated using standard non-compartmental techniques. Maximum plasma concentration and time to maximum plasma concentration were taken directly from the data. $T_{lag}$ was calculated by extrapolation of the straight line from the initial absorption curve. The area under the curve (AUC) value from 0-∞ was calculated by trapezoidal integration. The capsule of the current example showed a consistent delayed release profile with a mean lag-time of 1.2 hours and a $T_{max}$ range of 1.5-3 hours. The comparator immediate release tablet had a highly variable initial absorption with a

mean lag time of 0.5 hours and a $T_{max}$ range of 0.5-3 hours. As shown in the table below, the $AUC_{0-\infty}$ ratios show that bioavailability was significantly increased due to the synchronized and enhanced solubilization of the drug.

Please amend the second paragraph beginning on page 42 of the specification to read as follows:

Dissolution of pioglitazone HCl tablets of Example 15 containing compositions from example 15-1 to 15-3 were performed to demonstrate the extended release and solubilization of pioglitazone over various period of times. Each tablet containing 50 mg pioglitazone HCl in composition of example 15-1 to 15-3 was placed in a USP type II dissolution apparatus, 100 rpm, with 250 ml of pH 6.8 simulated intestinal fluid without enzyme (100 rpm, 37°C.) for 8 hours. At given time points, an aliquot of the dissolution medium was sampled and assayed for the concentration of pioglitazone released (solubilized). The concentration of pioglitazone released as a function of time from the tablets is summarized in FIG. 10. ~~Culmative~~ Cumulative increase in pioglitazone solubility over its intrinsic solubility at this pH ranges from about 36% increase for Example 15-1 to about 6-fold increase for Example 15-3. ranges.

Please amend the table on page 27 of the specification to read as follows:

| **Example** | **Solubilizer** | **Solubilizer Aqueous Concentration (% w/v)** | **Cilostazol Aqueous Concentration (µg/ml)** |
|---|---|---|---|
| Control | No solubilizer | 0% | 6.5 |
| 1-3 | Polysorbate 80 | 0.1% | 9.6 |
| 1-4 | d-alpha-tocopherol polyethylene blycol 1000 succinate/dl-alpha-tocopherol/medium chain monoglycerides (~~Capmul~~CAPMUL® MCM)/ethanol [2:1:2:1 ratio] | 0.1% | 15.8 |
| 1-5 | Polyoxyl 35 Castor Oil/Polyoxyl 40 | 0.2% | 20.3 |

| | | | |
|---|---|---|---|
| | Hydrogenated Castor Oil/Polysorbate 80/~~Labrasol~~LABRASOL®/medium chain monoglycerides (3:3:3:9:2 ratio) | | |
| 1-6 | d-alpha-tocopherol polyethylene glycol 1000 succinate/dl-alpha tocopherol (4:1 ratio) | 0.3% | 32.7 |
| 1-7 | d-alpha-tocopherol polyethylene glycol 1000 succinate/dl-alpha tocopherol succinate (4:1 ratio) | 0.3% | 31.2 |
| 1-8 | ~~Cremophor~~CREMOPHOR® RH40/d-alpha tocopherol succinate (3:2 ratio) | 1.2% | 57.3 |
| 1-9 | ~~Cremophor~~CREMOPHOR® EL/ d-alpha tocopherol succinate (3:2 ratio) | 1.2% | 29.9 |
| 1-10 | Polyoxyl 35 Castor Oil/Acetylated Monoglycerides/Polyvinylpyrrolidone K30* (1:1:1 ratio) | 4% | 79 |
| 1-11 | Polysorbate 80/Sorbitan monoleate (2:1 ratio) | 9% | 116 |

Please amend the table on page 31 of the specification to read as follows:

| **Component** | **Compositions (mg/dosage form)** | | | |
|---|---|---|---|---|
| | **5-1** | **5-2** | **5-3** | **5-4** |
| Cilostazol | 50 | 50 | 50 | 50 |
| d-alpha tocopherol polyethylene glycol 1000 succinate | 377 | 296 | 316 | 307 |
| Linoleoyl ~~Macrogolglycerides~~ Macrogolglycerides (~~Labrafil~~LABRAFIL® 2125CS) | 10 | 8 | 8 | 8 |
| Polyethylene Glycol 8000 | 20 | 16 | 0 | 0 |
| Clyceryl Dibehenate (~~Compritol~~COMPRITOL® 888 Ato) | 0 | 0 | 90 | 135 |
| HPMC K100M | 43 | 130 | 36 | 0 |

Please amend the second table on page 32 of the specification to read as follows:

| **Component** | **Compositions (mg/dosage form)** | |
|---|---|---|
| | **6-1** | **6-2** |
| Cilostazol | 25 | 25 |
| ~~Cremophor~~CREMOPHOR® RH40 | 125 | 128 |

| | | |
|---|---|---|
| HPMC K4M | 85 | 85 |
| Talc | 9 | 9 |
| Colloidal $SiO_2$ | 1 | 1 |
| Polyvinylpyrrolidone K90 | 45 | 45 |
| Sodium dodecyl sulfate | -- | 2.5 |

Please amend the table on page 34 of the specification to read as follows:

| Example | Components | Composition (% w/w) |
|---|---|---|
| 8-1 | ~~Cremophor~~CREMOPHOR® EL<br>Carvedilol | 94.0% w/w<br>6.0% |
| 8-2 | E-TPGS<br>Carvedilol | 94.0% w/w<br>6.0% |
| 8-3 | ~~Cremophor~~CREMOPHOR® EL<br>~~Labrafil~~LABRAFIL® 2125CS<br>Carvedilol | 75.2% w/w<br>18.8%<br>6.0% |
| 8-4 | E-TPGS<br>~~Compritol~~COMPRITOL® 888 Ato<br>Carvedilol | 75.2% w/w<br>18.8%<br>6.0% |
| **Comparative Example** | **Components** | **Composition** |
| Control | Carvedilol | 100.0% w/w |

Please amend the table on page 36 of the specification to read as follows:

| Component | Compositions (mg/dosage form) | |
|---|---|---|
| | **9-1** | **9-2** |
| Carvedilol | 25 | 25 |
| d-alpha tocopherol polyethylene glycol 1000 succinate (~~Vitamin~~VITAMIN E TPGS ®) | 221 | 210 |
| Clycerol Dibehenate (~~Compritol~~COMPRITOL® 888 Ato) | 55 | 53 |
| HPMC K1000LV | 59 | -- |
| HPMC K4MP | 59 | 56 |
| Carbopol 940 | -- | 56 |
| Amorphous Silica (Cab-O-Sil M5) | 1 | 1 |

Please amend the table labeled Example 12-1 on page 39 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |

| | |
|---|---|
| TPGS | 76 |
| Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888) | 19 |

Please amend the table labeled Example 12-2 on page 39 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| TPGS | 57 |
| Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888) | 38 |

Please amend the table labeled Example 12-3 on page 39 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| TPGS | 57 |
| Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888) | 19 |
| Glycerol Distearate (~~Precirol~~PRECIROL® ATO) | 19 |

Please amend the table labeled Example 12-5 on page 39 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| ~~Gelucire~~GELUCIRE® 44/14 | 76 |
| Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888) | 19 |

Please amend the table labeled Example 12-6 on page 39 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| ~~Gelucire~~GELUCIRE® 44/14 | 76 |
| Glycerol Distearate (~~Precirol~~PRECIROL® ATO) | 19 |

Please amend the table labeled Example 12-7 beginning on page 39 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| ~~Cremophor~~CREMOPHOR® RH40 | 76 |
| Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888) | 19 |

Please amend the table labeled Example 12-8 on page 40 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| ~~Cremophor~~CREMOPHOR® RH40 | 76 |
| Glycerol Distearate (~~Precirol~~PRECIROL® ATO) | 19 |

Please amend the table labeled Example 13-2 on page 40 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| TPGS | 60 |
| Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888) | 16 |
| Methocel K4M (HPMC) | 19 |

Please amend the table labeled Example 13-3 on page 41 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| TPGS | 68 |
| Glycerol Distearate (~~Precirol~~PRECIROL® ATO) | 8 |
| Methocel K4M (HPMC) | 19 |

Please amend the table labeled Example 13-4 on page 41 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| TPGS | 68 |
| Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888) | 8 |
| Glycerol Distearate (~~Precirol~~PRECIROL® ATO) | 8 |
| Methocel K4M (HPMC) | 11 |

Please amend the table labeled Example 13-5 on page 41 of the specification to read as follows:

| Compositions | (w/w) |
|---|---|
| Zafirlukast | 5 |
| TPGS | 60 |
| Glycerol Dibehenate (~~Compritol~~COMPRITOL® 888) | 17 |
| Methocel K100LV (HPMC) | 19 |